Structural Abnormalities of Subicular Dendrites in Subjects With Schizophrenia and Mood Disorders

Preliminary Findings

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Background: Postmortem studies of the subiculum from subjects with schizophrenia have detected smaller pyramidal cell bodies and diminished immunoreactivity for the dendritic protein, microtubule-associated protein 2. While these findings suggest that subicular pyramidal cell dendrites may be structurally altered in subjects with schizophrenia, this possibility had not been tested directly.

Methods: Rapid Golgi impregnation of archival brain specimens was used to compare the morphologic characteristics of subicular dendrites in subjects with schizophrenia (n = 13) and mood disorders (n = 6) with subjects without psychiatric disease (n = 8). The specimens were processed and analyzed by physicians blind to diagnosis. The extent of dendritic trees in the subiculum and fusiform gyrus was examined by Sholl analysis. Spine density on apical dendrites of subicular pyramidal cells was determined at a fixed distance from the cell body.

Results: Spine density and arborization of subicular apical dendrites were significantly related to diagnostic group. Spine density was significantly lower in the schizophrenia and mood disorder groups than in the nonpsychiatric group. Among the mood disorder cases, diminished spine density was apparently related to a strong family history of major psychiatric diseases. There were no significant effects of diagnostic group on Sholl analysis of nonapical subicular dendrites nor on Sholl analysis of dendrites of neocortical pyramidal cells in the fusiform gyrus.

Conclusions: We have observed an association between schizophrenia and major mood disorders and structural abnormalities of subicular apical dendrites. Further studies are needed to test this association in a larger sample and to evaluate the potential role of family history and of confounding factors, such as medications and chronic institutionalization.

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CONVERGENCE of functional and structural evidence presents elements of cerebral synapses as possible sites of neuropathological lesion in subjects with schizophrenia. Goldman-Rakic and Selemon,1 citing evidence for decreased cortical volume but normal neuronal number in subjects with schizophrenia,2 state, "Our view is that certain neurons are dystrophic and undergo atrophy of their neuronal processes... "1(p442) Olney and Farber3 cite evidence for diminished N-methyl-D-aspartate receptor–mediated transmission as a crucial factor in subjects with schizophrenia. Feinberg4 and Keshevan et al5 suggest excessive synaptic pruning as a possible cause of schizophrenia. Each of these hypotheses suggests a loss or alteration of synaptic targets. In the brain, axonal processes may form synapses on neuronal cell bodies, on other axons, or, in most cases, on dendrites. Dendritic synapses may be either on the shaft of the dendrite or on spinous processes that project from these shafts. More than 90% of all excitatory synapses in the central nervous system are on dendritic spines, and the structure of dendritic spines dictates their conductive properties. Thus, loss or alteration of spines would be expected to lead to abnormalities of glutamate transmission, even if presynaptic elements and postsynaptic receptors were maintained.6 Conversely, excitatory neurotransmission influences the size and shape of dendritic spines.

Indication for the study of structural abnormalities of dendrites also comes from reports of quantitative abnormalities in presynaptic proteins, which suggest possible alteration in the number or structure of synapses (eg, findings from the article by Young et al7). Such alterations would most likely be reflected in changes in both axon terminals and the dendrites on which they most
SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

All psychiatric subjects were long-term inpatients in state psychiatric hospitals; one young patient had been discharged at the time of death. Each subject’s brain had been sent to our institution for routine neuropathological evaluation. Autopsies were performed at 4 psychiatric hospitals and 1 medical examiner’s office. Six (46%) of the schizophrenia cases and 5 (83%) of the mood disorder cases were obtained from a single institution. The nonpsychiatric cases all were obtained from routine autopsies at Columbia-Presbyterian Medical Center, New York, NY. Cases were selected for similar age and postmortem interval in the 3 groups and for absence of Alzheimer disease or focal lesions in the hippocampal formation. Details are given in the Table. Informed consent was obtained for all autopsies either from the next of kin or, in the absence of family, by the medical director of the institution in which the patient resided.

CLINICAL EVALUATION

Clinical diagnoses were established by review of hospital records by a team of psychiatrists and psychologists blind to the autopsy results (J. K.). Diagnostic evaluations employed the modified Diagnostic Evaluation After Death, a medical record review protocol that has shown high inter-rater reliability (k = 0.643). All cases were reviewed by at least 2 raters. The reviews were discussed by the entire clinical diagnostic team, and consensus diagnoses were determined. The schizophrenia group included those subjects with a primary consensus diagnosis of schizophrenia (n = 11) or schizoaffective disorder (n = 2). The mood disorder group comprised 4 subjects with bipolar disorder, 1 with major depression, and 1 with depressive disorder not otherwise specified. The nonpsychiatric subjects were reviewed in the same manner as the psychiatric subjects and were included in the nonpsychiatric group only if there was no psychiatric diagnosis (n = 7) or if the only psychiatric diagnosis was an adjustment disorder (n = 1). Slightly fewer than half of the adult autopsy subjects at Columbia-Presbyterian Medical Center meet this criterion.

Subjects’ family histories were derived from notes in the subjects’ medical records and recorded in the modified Diagnostic Evaluation After Death by each rater. While all psychiatric records contained data on family history, these were not sufficiently detailed to allow rigorous application of DSM-IV criteria. No psychiatric illnesses were reported in the family histories of any of the subjects in the nonpsychiatric group.

NEUROPATHOLOGICAL EXAMINATIONS

Detailed neuropathological examinations were performed on all cases, as described previously. These included 2 diagnostic neuropathological reviews (with and without knowledge of demographic factors and clinical history) and an assessment of neuritic plaque and neurofibrillary tangle counts performed blind to all clinical and other neuropathological information.

GOLGI IMPREGNATION

The protocol for rapid Golgi impregnation (Leisa Glantz, PhD, e-mail communication, December 18, 1995) was modified from that previously described by Lund. From brains that had been fixed in formalin for 4.2 to 12.5 years, a 4-mm thick coronal block of the left hippocampus and subiculum (at the level of the lateral geniculate body) was impregnated in succession (over 18 days) with potassium dichromate and osmium tetroxide, graded solutions of silver nitrate, and collodion. Sections were cut at 90 µm. In most cases (11 of 13 in the schizophrenia group, 5 of 6 in the mood disorder group, and 6 of 8 in the nonpsychiatric group), the block extended sufficiently far laterally to include a portion of the fusiform gyrus (Figure 1).

Specimens from the 3 diagnostic groups were processed simultaneously, without knowledge of the clinical diagnosis. The cases were coded and reviewed in a random order, blind to diagnosis. Blindness was maintained throughout analysis.

ANALYSIS OF GOLGI STAIN

From the subiculum of each subject (restricted to the area of the subiculum where the Golgi stain clearly allowed the distinction of external and internal pyramidal cell layers), and from the neocortex in those blocks that extended to the fusiform gyrus, the cell bodies and dendrites of the 5 best-impregnated internal pyramidal cells (or in neocortex layer V pyramidal neurons) were traced in 3 dimensions at magnification ×200 on a microscope (Leitz, Stuttgart, Germany) with a motorized stage (Ludl Electronic Products, Hawthorne, NY) and a computer display projected into the viewing field of the microscope (Lucivid; MicroBrightField, Colchester, Vt). Tracing employed the program NeuroLucida (MicroBrightField). Dendritic tracings were quantified by Sholl analysis, performed by the NeuroLucida software. This procedure constructs a series of equally spaced, spherical shells around the center of the cell body and then determines the number of dendritic processes intersecting each successive shell (ie, at each radius). Apical and basilar dendrites are treated separately. For analysis, each case was represented by the average value at a given shell radius for apical or basilar dendrites of all traced neurons in a given anatomical region (ie, subiculum or fusiform gyrus).

Spines were counted on the main shaft of the apical dendrite of 5 neurons in the internal pyramidal layer of the subiculum. Counts were made manually at magnification ×600 between 50 µm, and 100 µm from the cell body, as measured with a calibrated eyepiece graticule.

STATISTICAL ANALYSIS

Data from Sholl analyses were analyzed by 2-tailed permutation test with the log likelihood ratio from mixed-model analysis as the test statistic. Four such analyses were performed, since each region (subiculum and fusiform gyrus) and each type of dendrite (apical and nonapical) was considered separately. When the result was statistically significant (α = .05), the analysis was repeated with each pair of groups, and the P values were multiplied by 3 to correct for multiple comparisons. Spine densities were compared by 2-tailed Kruskal-Wallis and Mann-Whitney tests.
commonly form synapses. Smaller cell bodies of subicular and hippocampal pyramidal cells\(^8,9\) may reflect diminished support of neuronal processes. Diminished immunoreactivity in subjects with schizophrenia for microtubule-associated protein 2 (MAP2),\(^{10,11}\) an important determinant of dendritic structure and plasticity, further suggests the possibility of structural abnormalities of dendrites, either as a cause or an effect of alterations in MAP2. This loss of MAP2 immunoreactivity is localized to the entorhinal cortex and subiculum, which relay inputs and outputs, respectively, between the adjacent hippocampus and various neocortical regions. Impaired subicular function could thus produce a disturbed relationship between emotion and thought, a fundamental feature of schizophrenia.\(^12\)

**Characteristics of Diagnostic Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonpsychiatric Subjects (n = 8)</th>
<th>Subjects With Schizophrenia (n = 13)</th>
<th>Subjects With Mood Disorder (n = 6)</th>
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<td>Sex, M/F</td>
<td>3/5</td>
<td>10/3</td>
<td>2/4</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>61.5 ± 11.2</td>
<td>65.9 ± 17.3</td>
<td>66.9 ± 9.6</td>
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<tr>
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<td>NA</td>
<td>26.3 ± 9.6</td>
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<tr>
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<td>NA</td>
<td>39.5 ± 12.0</td>
<td>28.0 ± 18.3</td>
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<td>23.1 ± 21.3</td>
<td>29.8 ± 17.6</td>
<td>19.2 ± 10.0</td>
</tr>
<tr>
<td>Fixation, d</td>
<td>2482 ± 181</td>
<td>3038 ± 757</td>
<td>2604 ± 912</td>
</tr>
<tr>
<td>NFT†</td>
<td>4.4 ± 6.0</td>
<td>2.6 ± 3.5</td>
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Somatic treatments,

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<tr>
<td>Electroconvulsive</td>
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<td>5</td>
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</tr>
<tr>
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<td>0</td>
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<tr>
<td>Lithium</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>0</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>Anticholinergics</td>
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<td>7</td>
<td>2</td>
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<tr>
<td>Sedatives</td>
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<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Other somatic treatments</td>
<td>(eg, insulin coma)</td>
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<td>7</td>
</tr>
<tr>
<td>Any lifetime neuroleptic exposure</td>
<td>0</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Neuroleptics within 12 mo of death</td>
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Substance abuse,

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<td>Alcohol</td>
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<td>0</td>
<td>1†</td>
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<tr>
<td>Tobacco use, No. of cases</td>
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<td>9</td>
<td>4</td>
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</tbody>
</table>

* M indicates male, F, female; NA, not applicable; PMI, postmortem interval; and NFT, neurofibrillary tangles. Values are given as mean ± SD except where indicated.
† NFTs in field >250 of maximum density in hippocampal formation at level of lateral geniculate body.\(^21\)
‡ Same subject abused alcohol.

Golgi impregnation permits examination of dendritic structure at the light microscopic level. The few Golgi studies in subjects with schizophrenia report loss of spines in neocortical pyramidal cells\(^13,14\) and dendritic abnormalities in the orbitofrontal cortex\(^15\) and brainstem reticular formation.\(^16\) Studies using electron microscopy demonstrate smaller spines\(^17\) and altered distribution of spines\(^18\) in the striatum. No Golgi or electron microscopic study has examined dendrites in the subiculum. We therefore compared this region in autopsy tissue from individuals who had been institutionalized for schizophrenia or mood disorders with a third group of individuals who had not experienced psychiatric disease.

**RESULTS**

As measured by Sholl analysis (Figure 2), apical dendritic trees of subicular internal pyramidal cells were less extensive in the schizophrenia and mood disorder groups than in the nonpsychiatric group (permutation test, \(P = .04\)), while there were differences among groups neither for basilar dendrites of these cells (\(P = .45\)) nor for apical (\(P = .37\)) or basilar (\(P = .36\)) dendrites of neocortical pyramidal cells. Pairwise analysis of subicular apical values, corrected for 3 comparisons, yielded a significant difference (\(P = .06\)) between the schizophrenia and nonpsychiatric groups but not between the mood disorder and nonpsychiatric groups (\(P = .25\)) or the mood disorder and schizophrenia groups (\(P > .99\)).

**APICAL DENDRITIC SPINES**

The density of spines on apical dendrites of subicular internal pyramidal cells was markedly reduced in subjects with schizophrenia. This was readily apparent on
There was a significant effect of diagnosis on spine density (Kruskal-Wallis $\chi^2 = 14.3$, $P < .001$), with significant differences between nonpsychiatric subjects and subjects with schizophrenia ($U = 0, W = 78, P < .001$, corrected for 3 comparisons) or subjects with mood disorder ($P = .04$) but not between subjects with mood disorder and schizophrenia ($P > .99$). There was no overlap between schizophrenia cases and nonpsychiatric cases, but the mood disorder cases were distributed bimodally, overlapping both groups (Figure 4).

Among the 6 subjects with mood disorder, 3 had spine densities similar to the nonpsychiatric cases, while 3 had spine densities similar to those of the subjects with schizophrenia. Although these numbers are too small to allow statistically meaningful observations, we reviewed the case histories carefully for distinguishing characteristics. The 2 groups did not differ in terms of age, sex, disease duration or severity, bipolarity, psychotic features, or treatment history. However, all 3 subjects with low spine density had at least 2 first-degree relatives with definite or probable mood disorders or schizophrenia (10 affected first-degree relatives, 9 of whom were treated in state psychiatric hospitals), while the 3 subjects with higher spine densities had no such relatives. Among the subjects with schizophrenia, there was no relationship between family history and dendritic spine density. The 2 subjects with schizoaffective disorder were typical of the schizophrenia group.

**POTENTIALLY CONFOUNDING FACTORS**

The 3 groups were similar regarding age, postmortem interval, and fixation interval, and within the range encountered in this study, there was no correlation between these factors and spine density or Sholl analysis. (For subicular apical dendritic intersections at a radius of 140 $\mu$m vs postmortem interval, $r_{26} = -0.15, P = .45$ vs fixation interval, $r_{26} = -0.04, P = .85$. For spine density vs postmortem interval, $r_{25} = -0.23, P = .26$ vs fixation interval, $r_{23} = -0.07, P = .73$. Similar results are obtained if diagnostic groups are analyzed individually.) No differences between men and women were apparent in any group.

All of the subjects in psychiatric groups had been treated with neuroleptic drugs. There was no apparent relationship between neuronal dendritic structure and the use of neuroleptic drugs within 1 year of death. Other somatic treatments were also common (Table): all of the subjects with mood disorder and all but one of the subjects with schizophrenia had received at least 1 of these treatments and most had received several. No treatment was associated with significant differences, within the schizophrenia group alone or within both
Structural abnormalities of subicular dendrites were found in a group of institutionalized subjects with schizophrenia and mood disorders. This finding is consistent with current theories regarding synaptic dysfunction in subjects with schizophrenia and could be either the cause or the result of such dysfunction. If the loss of apical dendritic spines is primary, postsynaptic proteins determining the size and shape of dendritic spines would be promising candidates for future biochemical and genetic studies.

The major inputs to the subiculum are from the CA1 field of the hippocampus via the alveus and from the entorhinal and adjacent transitional cortical areas via the

Figure 3. Apical dendrites of subicular internal pyramidal neurons, 100 µm from origin of dendrite. A, C, and E, Nonpsychiatric subjects: males, aged 43 and 64 years; and female, aged 72 years, respectively. B, Subject with schizoaffective disorder: male, aged 39 years. D and F, Subjects with schizophrenia: males, aged 46 and 68 years, respectively. Apical dendrites in subjects in the schizophrenia group contain small numbers of spines (B) or nearly none (D and F) (Golgi stain; bar = 10 µ).
perforant pathway. The positions of the afferent fibers are such that those from the hippocampus are more likely to synapse on the basilar dendrites of subicular pyramidal cells, while those from the entorhinal cortex are more likely to synapse with the apical dendrites of these cells. Other inputs to subicular apical dendrites are probably provided by subicular interneurons, dopaminergic projections from ventral tegmental area and medial pars compacta of the substantia nigra, and cholinergic projections from the amygdala, although these last 2 vary considerably within the mediolateral extent of the subiculum and the adjacent prosubiculum and presubiculum. The hippocampus contributes some fibers directly to the fornix, but most hippocampal output is relayed through the subiculum. Thus, while ablation of the subiculum, or a lesion involving the basilar dendrites or axons of its pyramidal cells, might be expected to interrupt this pathway and produce an amnestic syndrome, a lesion primarily involving apical dendrites would be more likely to affect the modulation of this output and to give rise to less predictable functional consequences.

We performed spine counts only on the apical dendrites of subicular internal pyramidal cells. Others have reported decreased numbers of spines on dendrites (apical and basilar combined) of pyramidal cells in the prefrontal cortex and temporal pole and on the basilar dendrites of pyramidal cells in the prefrontal cortex but not in the primary visual cortex. Although the differences in these areas are not so large as in the subiculum, further study is needed to determine the degree to which this abnormality is localized.

We found considerable morphological overlap between institutionalized subjects with schizophrenia and those with mood disorders. Regarding loss of spines, there was no overlap between the subjects with schizophrenia and control subjects. However, the values for the 6 subjects with mood disorder were split between 3 subjects whose values overlapped with those for the nonpsychiatric subjects and 3 whose values fell within the lower half of the values for the subjects with schizophrenia. Each of the 3 subjects with mood disorder with low spine density had at least 2 first-degree relatives with definite or probable schizophrenia or major mood disorder, while there were no such relatives among the 3 subjects with mood disorder with higher spine densities. The results must be interpreted with caution since the number of cases is small and the collection of family history was limited to review of the probands’ medical records, a known pitfall. However, the findings suggest an overall similarity between schizophrenia and familial mood disorders.

Other recent studies found structural abnormalities of the hippocampal formation that may be similar in subjects with schizophrenia and subjects with mood disorders. One magnetic resonance imaging study revealed diminished left hippocampal volume in both first-episode schizophrenia and first-episode affective psychosis (although another magnetic resonance imaging study of first-episode cases found the reduction only in subjects with schizophrenia). Markedly reduced numbers of nonpyramidal cells in the CA2 field of the hippocampus were found in both subjects with schizophrenia and bipolar disorder, again raising long-standing questions about whether schizophrenia and mood disorders are distinct entities.

Reduced volume and glial cell number have been reported in the subgenual prefrontal cortex of subjects with familial mood disorders, while absent in subjects with nonfamilial mood disorders. In these studies, subjects with familial mood disorder had relatives with mood disorders; data regarding relatives with schizophrenia were not presented. However, familial associations between schizophrenia and mood disorders are sufficiently strong to allow suspicion of a common genetic influence among some cases of each disease.

Neuroleptic drugs are a potential confounding factor. All subjects with schizophrenia or mood disorder had been treated at some point with these drugs. Two subjects in each psychiatric group had not received neuroleptic drugs within 1 year of death, and these subjects had the same abnormalities as the others. Nonetheless, we cannot rule out the possibility that neuroleptic exposure accounts for the diminished arborization. Experimental studies of the effects of neuroleptic drugs on synaptic structures have focused on the striatum, where the density of dopamine type 2 receptors is greatest. In rats, 3 weeks of treatment with haloperidol increased the synaptic area or number in the striatum but not in the CA1 field of the hippocampus. Spine density in the striatum increased after 3 weeks but decreased after 6 months of haloperidol treatment. In layer VI of the medial prefrontal cortex, spine density decreased after 16 weeks of treatment with haloperidol (3 mg/kg per day) but was unchanged after 1 year at a lower dose (1.5 mg/kg per day). It is possible that neuroleptic drugs and psychiatric disease both contribute to dendritic remodeling and that this process contributes to the therapeutic and adverse effects of the drugs. It is also possible that institutionalization alone may affect dendritic structure, perhaps as a result of sensory deprivation. Furthermore, we cannot rule out the possibility that other treatments contributed to our results, either alone or in combination.

It must also be noted that rapid Golgi impregnation of human postmortem material is an imperfect pro-
cEDURE. Composed with material from experimental animals, dendritic trees appear less extensive; this has been attributed to postmortem delays, although no consistent differences have been found among the postmortem delays encountered in human tissue.48,49 Among the intervals that we encountered, there was no effect of postmortem delay on dendritic structure, the 3 groups were similar in terms of postmortem delay, and the differences in the extent of dendritic trees were not found in basilar dendrites or in neocortical neurons. Nonetheless, it would be worthwhile to repeat these studies using Golgi-Cox impregnation of fresh tissue, which may be less susceptible to postmortem delay. 46 (Golgi-Cox impregnation is not applicable after prolonged fixation, while a minimum of 6 months’ fixation is reportedly necessary for use of the rapid Golgi method. 45) Finally, the impregnation of only a limited number of neurons is inherent to these methods; while allowing the tracing of processes, this restricts the possibility of random sampling of neurons.

Despite these limitations, this study demonstrates dramatic structural abnormalities in the subicular neurons of individuals with schizophrenia, which are shared by some individuals with mood disorders. The loss of dendrites and spines is consistent with current theories of the pathophysiological function in schizophrenia, and its presence in the subiculum has important functional implications. Other methods should be employed to test this finding, and larger samples should be examined to evaluate the potential roles of family history and somatic treatments.

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References


